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Long-term response to continuous duodenal infusion of levodopa/carbidopa gel in patients with advanced Parkinson disease: The Barcelona registry

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ABSTRACT

Introduction: Continuous infusion of levodopa/carbidopa intestinal gel (LCIG) is an effective treatment for patients with advanced Parkinson Disease (PD) that cannot be further improved by oral therapy.
Methods: We conducted an observational, prospective, and multicenter study to collect, in a large sample of PD treated with LCIG, long-term information about the outcome and safety of the treatment. The assessments were performed before LCIG, 1, 3, 6 months after, and ever since, every 6 months.
Results: We studied 72 patients with a mean observation time of 22 months and a maximum of 48 months. During follow-up 28 patients discontinued the treatment, especially for lack of efficacy or adverse events related to the drug. We obtained a significant improvement of motor and non-motor fluctuations, mean off time and some non-motor symptoms. A significant increase in the percentage of time with dyskinesias was found in patients having less than 50% of the day with dyskinesias before LCIG. However, patients having already many dyskinesias before LCIG experienced a significant decrease of the troublesome dyskinesias, meaning that outcomes might be different depending on specific clinical characteristics. Adverse effects were in general minor but one case of intestinal perforation and one of abdominal cellulite were observed.
Conclusions: We confirmed that LCIG is a very effective treatment option for advanced PD; however considering the findings that dyskinesia can increase and the potential for serious side effects, we suggest the necessity for development of guidelines that better define the profile of responders.

1. Background

Substitutive oral dopamine (levodopa) is the best treatment for Parkinson's disease (PD) symptoms; however, after an initial "honeymoon" period of time with a sustained response, long-term treatment might induce the appearance of clinical fluctuations and dyskinesias [1,2]. These complications over time may become

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severe and difficult to treat with the consequent worsening of the patient quality of life. The origin of these complications is unknown, but a relationship with the pulsatile dopaminergic stimulation, due to the oral substitute therapy, has been proposed [3]. In a way to give a more stable and physiological stimulation to the dopaminergic receptors, alternative therapy, as continuous subcutaneous infusion of apomorphine, deep brain stimulation (DBS) [4,5], and the continuous intra-duodenal infusion of levodopa-carbidopa gel (LCIG) have been tried [6].

LCIG is a water-based suspension containing micronized levodopa 20 mg/ml and carbidopa 5 mg/ml that was approved in EU in 2004 as treatment for advanced PD. Since its approval substantial amounts of information regarding its efficacy and security have been collected, but so far there are only two controlled studies [7,8], and the long-term information is still scarce and incomplete [9–13].

The aim of this study was to record, from a large group of patients, prospectively, in a routine clinical setting, comprehensive long-term (up to 48 months) clinical data on efficacy and safety of LCIG.

2. Methods

We conducted an observational, prospective, and open label study in the context of the clinical practice of 5 centers of the metropolitan area of Barcelona. The study protocol was approved by the Ethics Committee of Hospital Clinic of Barcelona (Barcelona, Spain) and procedures were in accordance with the ethical standards laid down in Helsinki Declaration, and revised in 2000. All patients signed a consent form for the procedure and for the collection and the report of data. We enrolled 72 PD patients, all with motor fluctuations, not satisfactory controlled by the standard treatment. The LCIG starting procedure was performed, in all centers following three steps: test period, percutaneous endoscopic gastrostomy (PEG) surgery, and post PEG evaluation. During the first days of hospitalization, we calculated the dose of LCIG to administer from the oral dose of levodopa and dopamine agonist, by using the levodopa equivalent daily dose (LEDD) [14]. Then we performed a test phase, where a nasoduodenal tube connected to a portable pump administered the treatment. After that, the PEG was done and the infusion started trough a catheter ending in the duodenum. Finally, after PEG, the infused therapy was optimized following the patient's condition. Patients were evaluated before LCIG (baseline visit), 1, 3, and 6 months after the procedure and since ever, every 6 months until a maximum follow up of 48 months. During the entire follow up the dose was optimized according to the patient's requirements.

During each visit we recorded clinical data, and information about daily perfusion and oral treatment dosage. To collect clinical data we used a not-validated semi-structured interview that explores the presence (yes or not) and severity (mild, moderate or severe) of different items. Information was recorded about motor (wearing-off, delayed on, no-on, unpredictable off, nocturnal and morning akinesia, hours/day spent in off), and non-motor fluctuations (dysautonomic symptoms, such as hyperhidrosis and palpitations, sensitive symptoms, such as pain and paresthesia, and every other non motor symptoms observed in off state). We assessed then the presence, the duration (hours/day spent with them) the severity (using the item 33 of UPDRS-IV) and the timing (on, off state or transitional) of dyskinesias. The presence and severity of non motor symptoms were recorded by classifying them in neuropsychiatric symptoms (presence and severity of depression, cognitive impairment, dementia, hallucinations/psychosis, symptoms of dopaminergic dysregulation), sleep disorders (presence and severity of insomnia, excessive daytime sleepiness, nightmares and dream enacting behaviors), dysautonomic symptoms (presence and severity of urgency/incontinence, constipation, orthostatic hypotension), and others (presence and severity of pain, fatigue and restless leg syndrome). As general indicator of disease progression and treatment response over time both the investigator and the patients performed the Clinical Global Impression Scale (CGI) [15]. Clinical data included also the results of the assessment of UPDRS part I-IV (part motor-III performed in on and off state) [16], and Schwab and England Activities of Daily Living Scale [17] both on and off therapy. Finally we collected all information about safety, in terms of occurrence, timing and severity of adverse events (AEs).

Results were expressed as mean and standard deviation for continuous variables and as absolute numbers and relative frequencies (%) for categorical variables. Due to the variation in the duration of follow-up, for each variable the mean last value reported during the last visit (LV) was calculated and compared to mean baseline. Comparisons in the clinical variables between visits were conducted using a Student's t-test for continuous variables and Pearson's chi-squared test, McNemar test or Fisher exact test for categorical variables. Statistical significance was set at a p-value of $p < 0.05$. The statistical analysis was performed using SAS v.9.3 (SAS Institute Inc., Cary, North Carolina).

3. Results

The study was conducted from May 2008 to August 2012. We enrolled 72 PD patients: center 1 enrolled 23 patients, center 2, 17 patients, center 3, 16 patients, center 4, 11 patients and center 5, 5 patients. Characteristics of the patients are presented in the Table 1. The test phase was different depending on the center, with a mean duration of 5 days (minimum 3 days, maximum 10 days). The mean follow up was 22 ± 14 months. Of the 72 patients, three reached the 48 months-evaluation, 12 the 36 months-evaluation, 17 the 24 months, 19 reached the scheduled follow-up evaluation of 18 months and in 21 patients the follow-up ranged between 1 and 14 month. During the study, 28 patients discontinued the treatment, the major part of them in the first year of inclusion. Fifteen patients discontinued in the first three months after starting LCIG. Over the 28 drop outs, thirteen were related to lack of efficacy of the therapy, 8 for the occurrence of adverse events (AEs) related to the therapy (i.e. severe dyskinesias, bothersome sleepiness, symptomatic orthostatic hypotension, anorexia, and uncontrolled punding), four abandons were for lack of acceptance of the device, and three for AEs related to the PEG and to the device (Table 2 and Fig. 1). The patients who dropped out from the study did not differ in terms of age, sex distribution, and severity of the disease compare to other patients. However those patients that drop out from the study had slightly more dyskinesias compare to the rest of the population ($p > 0.05$).

3.1. Motor and non-motor fluctuations

From baseline to LV we observed a significant decrease of the number of patients reporting wearing-off (97% vs. 64%), delayed on (86% vs. 28%), no-on (56% vs 18%), unpredictable off periods (75% vs. 29%), nocturnal akinesia (73% vs. 49%) and morning akinesia (78% vs. 47%) ($p < 0.0001$). The mean OFF time per day decreased significantly from 6.8 ± 2.8 h before treatment to 3.0 ± 3.5 h in the LV and the percentage of the day in off decreased significantly from 45% before treatment to 20% in the LV ($p < 0.0001$). Behavioral and mood disorders, especially anxiety, depression and irritability reported at baseline by the 66% of patients, decreased during LV to 38% ($p < 0.0001$); the % of patients with dysautonomic symptoms, especially hyperhidrosis, decreased from 60% to 33% ($p = 0.0015$);

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